

Application and research progress of BCL2 inhibitors in elderly patients with hematologic malignancies

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Abstract

Apoptosis is a process of programmed cell death which mediated by proteases called caspases. Deregulated apoptosis is the basis of a variety of diseases, including cancer. The pathways of apoptosis can be divided into two independent signaling pathways, intrinsic or extrinsic. B-cell lymphoma 2 family proteins including BCL2 anti-apoptotic protein play an important role in the regulation of caspases in intrinsic pathways. Since that BCL2 is often overexpressed in cancer cells, a series of inhibitors targeting the BCL2 family antiapoptotic proteins have been developed to induce apoptosis in cancer cells. The highly selective BCL2 inhibitors, such as venetoclax (ABT-199, Venclexta™) and navitoclax(ABT-263), have shown good efficacy and safety in many hematologic malignancies. Considering that elderly patients with hematological malignancies still lack effective treatments, BCL2 inhibitors are undoubtedly an attractive new therapy due to their desirable safety and efficacy. This article reviews the application and research progress of BCL2 inhibitors in elderly patients with hematologic malignancies.

Keywords: BCL2 inhibitors, hematologic malignancies, venetoclax, elderly patients

Introduction

The treatment of hematologic malignancies remains challenging in the elderly population. The incidence of hematologic malignancies keeps stable in the young and increases gradually in the elderly. With the application of intensity therapies such as chemotherapy, the survival rate of young people with hematologic malignancies continues to increase [1, 2] while the survival rate of the elderly remains almost unchanged [3]. Older patients were poorly prepared due to comorbidities and cytogenetic abnormalities [4, 5]. Also, older patients often show intolerance to standard treatments such as chemotherapy, and the prognosis is poor with non-transplant therapy. Treatment methods suitable for this population are still being explored. BCL2 (B cell lymphoma gene 2) family of proteins can be classified into two subfamilies, pro-apoptotic and

anti-apoptotic proteins. The proapoptotic BCL2 family proteins consist of the BH123 and BH3-only proteins whereas the antiapoptotic BCL2 family protein consists of BCL2 and its close relatives BCL-xL, MCL1, BCL-W, BCL-B and BCL2A1. The intrinsic apoptotic pathways are associated with the exudation of cytochrome C from mitochondria. The anti-apoptotic BCL2 protein blocks the efflux of cytochrome C and other mitochondrial intermembrane space proteins by blocking the pro-apoptotic BCL2 family members BAX and/or BAK induced by BH3 protein in the mitochondrial outer membrane. Upregulation of BCL2 expression has been demonstrated in many cancers, including multiple hematological malignancies. More importantly, overexpression of BCL2 is associated with resistance to radiotherapy and chemotherapy. This suggests that targeting BCL2 may play an important role in antitumor therapy.

BCL2 inhibitor is a kind of BH3 mimetics that target anti-apoptotic proteins in tumors to promote the initiation of the intrinsic apoptotic pathways. The BCL2 inhibitors currently under study are GX15-070/obatoclax, ABT-737, ABT-263/navitoclax, ABT-199/venetoclax, etc [6]. Numerous preclinical and clinical trials have demonstrated that BCL2 inhibitors can play a role in the treatment of variety of hematologic malignancies. Venetoclax in

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combination with azacitidine, decitabine, or LDAC has already approved by the United States Food and Drug Administration (FDA) for use in untreated patients with AML who are 75 years or older or who have comorbidities that preclude the use of intensive induction chemotherapy. This article reviews the application and research progress of BCL2 inhibitors in elderly patients (over 60 years old) with hematologic malignancies. Table 1 shows the research progress of BCL2 inhibitors.

Application of BCL2 inhibitors in elderly patients with acute myeloid leukemia

Preclinical trials of BCL2 inhibitors in acute myeloid leukemia(AML)

(1) Monotherapy

Venetoclax showed effective lethality against AML cells in preclinical trials. A preclinical trial [7] demonstrated in vivo and in vitro that ABT-199 (venetoclax) was lethal to AML cells. The AML cell lines were exposed to increasing concentrations of ABT-199 for 48 h. Cell growth was observed to be inhibited and apoptosis was observed within several hours, demonstrating AML cells were sensitive to venetoclax.

(2) Combination therapy

A trial [8] compared the synergistic effect of ABT-737 versus ABT-199 with 5-azacytidine(5-Aza) in myeloid malignancies using short-term ex vivo cultures of primary AML and MDS/chronic myelomonocytic leukemia (CMML) samples. ABT-199 produces 5-Aza sensitization similar to that of ABT-737 for AML and MDS in vitro.

Table 1. Ongoing clinical trials with BCL2-inhibitor in AML, NHL, MM, MDS.

Clinical trial	Conditions	Study design	Intervention
NCT03672695	Acute Myeloid Leukaemia	Phase 1	S 64315 (MIK665)+venetoclax
NCT03390296	Recurrent/Refractory Acute Myeloid Leukemia	Phase 1 Phase 2	OX40, Venetoclax, Avelumab, Glasdegib, Gemtuzumab Ozogamicin, and Azacitidine
NCT03214562	High Risk Myelodysplastic Syndrome Recurrent/Refractory Acute Myeloid Leukemia	Phase 1 Phase 2	Venetoclax + Chemotherapy
NCT04070807	Acute Myeloid Leukaemia	Observation	
NCT04150029	Acute Myeloid Leukaemia	Phase 2	MBG453 + Venetoclax + Azacitidine
NCT04501120	Relapsed/Refractory Acute Myeloid Leukaemia	Phase 1 Phase 2	APG-2575 + reduced-dose HHT + standard-dose HHT + Azacitidine
NCT04128501	Acute Bilineal Leukemia Acute Biphenotypic Leukemia Acute Myeloid Leukemia Blasts More Than 5 Percent of Bone Marrow Nucleated Cells Minimal Residual Disease Mixed Phenotype Acute Leukemia T Acute Lymphoblastic Leukemia Therapy-Related Acute Myeloid Leukemia	Phase 2	Azacitidine+ Venetoclax
NCT04092179	Acute Myeloid Leukemia Relapsed Cancer Refractory Cancer IDH2 Gene Mutation	Phase 1 Phase 2	Enasidenib + Venetoclax
NCT03471260	High Risk Myelodysplastic Syndrome IDH1 NP_005887.2:p.R132X Myeloproliferative Neoplasm Recurrent Acute Myeloid Leukemia Refractory Acute Myeloid Leukemia	Phase 1 Phase 2	Azacitidine + Ivosidenib + Venetoclax
NCT04424147	Relapsed/Refractory Acute Myeloid Leukaemia	Phase 2	Azacitidine + Venetoclax (HVA regimen)
NCT03755154	Relapse or Refractory Acute Myeloid Leukemia Relapse or Refractory Non-Hodgkin Lymphoma Relapse or Refractory Multiple Myeloma Relapse or Refractory Chronic Lymphocytic Leukemia	Phase 1	S65487
NCT03713580	Non-Hodgkin Lymphoma	Phase 1	Venetoclax
NCT02877550	Follicular Lymphoma	Phase 1	Obinutuzumab + Venetoclax
NCT03113422	Follicular Lymphoma Non-Hodgkin's Lymphoma Follicular Non-Hodgkin's Lymphoma, Adult High Grade	Phase 2	Venetoclax

This indicates that both ABT-199 and ABT-737 can be used in combination with 5-Aza to fight acute myeloid leukemia.

Clinical trials of BCL2 inhibitors in AML

(1) Monotherapy

A phase II, single-arm study [9] recruited 32 patients (median age was 71) with relapsed/refractor AML or untreated AML unfit for intensive therapy. Single-agent venetoclax showed an objective response rate of 19% in patients with swith heavily pretreated AML, according to IWG criteria. The other 19% of patients had antileukemic activity, presenting with partial bone marrow response and incomplete blood recovery that did not meet the standard response criteria. The study showed that venetoclax as a single agent in AML had an acceptable safety profile. However, venetoclax as a single drug does not appear to show a high remission rate for patients.

(2) Combination therapy

The combination therapies were shown to be more effective in AML patients than monotherapy.

In a non-randomized, open-label, phase 1b study [10], venetoclax was tested in combination with decitabine, azacitidine and CYP3A inhibitor posaconazole in 57 patients over 65 years old. The dose cohorts are 400 mg, 800 mg, 1200 mg for venetoclax. In total, 43 (84%) of 51 patients had more than 80% reduction in bone marrow blasts, for those in the 400 mg and 800 mg cohorts of groups A and B, 27 (79%) of 34 patients had more than 80% bone marrow blast reduction. The results of this dose-increasing study showed that these drug combinations were well tolerated. Early mortality was reduced and there was good clinical activity in terms of overall response and overall survival in a patient population with historically poor treatment outcomes.

A single-center, phase II trial [11] with 168 patients over 65 years old also tested venetoclax combined with decitabine. The treatment plan was decitabine 20 mg/m² intravenously for 10 days with oral venetoclax 400 mg daily for induction, followed by decitabine for 5 days with daily venetoclax for consolidation. The overall response rate was 74% (125/168) and in each disease subgroups as follows: 89% in newly diagnosed AML (62/70), 80% in untreated secondary AML (12/15), 61% in treated secondary AML (17/28), and 62% in relapsed or refractory AML (34/55) ELN favorable and intermediate-risk AML, and IDH1mut or IDH2mut AML subgroups had good responses. However, there was no significant improvement in the TP53mut subgroup. The study showed that venetoclax with 10-day decitabine was tolerable in older patients. It shows higher activity in newly diagnosed AML and certain molecularly defined subgroups of relapsed or refractory AML.

Venetoclax, as a cytochrome P450 3A (CYP3A) substrate, may interact with CYP3A inhibitor when used in conjunction with CYP3A inhibitors [12]. When patients using BCL2 inhibitors are givenazole drugs to prevent

fungal infections, there may be a risk of drug interactions. A drug-drug interaction (DDI) substudy [13] including 12 patients over 65 years old were done to explore the interaction between venetoclax and posaconazole. The results showed that 50-100 mg posaconazole did not increase the risk of adverse reactions which supported using antifungal prophylaxis in AML patients treated with Venetoclax after a reduction of at least 75% of the dose. The trial shows that it is necessary to pay attention to the dosage adjustment when using these two drugs simultaneously.

Exploring the efficacy of BCL2 inhibitors in patients with different gene mutation types will help to further achieve precision therapy. A retrospective study [14] of 32 patients with TP53-mutated AML treated with venetoclax and hypomethylating agents (VEN/HMA) showed good results. The median age of patients is 68 years old. 16 (52%) patients among 31 evaluable patients experienced a response, including 7 CR and 9 CRi. The median leukemia-free survival for the responders was 234 days and the overall survival was 329 days. In patients with more than one TP53 mutation and in those who were treated with VEN/HMA in the frontline setting, CR/CRi rates showed an upward trend. The drug is promising in patients with R/R TP53m AML. The preliminary results of VEN/HMA were favorable, but the median LFS was relatively short and recurrent frequently. The VEN/HMA combination could be used to buy more remission time for patients undergoing transplantation.

A Phase Ib/II Study [15] tested venetoclax combined with low-dose cytarabine(LDAC) in adults over 60 years old with previously untreated AML ineligible for intensive. Eighty-two patients were enrolled in the 600 mg Venetoclax cohort with a median age of 74 years. Fifty-four percent of patients achieved complete remission (CR) or CR with incomplete blood count recovery(CRi). Differences in survival were observed among patients with different gene mutations. CR/CRi rates in patients with NPM1 or IDH1/2 somatic mutations were higher than average (89% and 72%, respectively), while CR/CRi rates were lower in patients with TP53 or FLT3 mutations (30% and 44%, respectively). The results indicated that venetoclax combined with LDAC has a manageable safety profile. It is believed to produce rapid and lasting remission for elderly AML patients who are not suitable for intensive chemotherapy.

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial [16] was done to verify the efficacy of azacitidine plus Venetoclax in previously untreated AML. The 431 patients were divided into the intervention group and the control group by a ratio of 2:1. The median age is 76. In the Venetoclax group, 66.4% of patients achieved a comprehensive complete response, compared with 28.3% in the control group. In patients with IDH1 or IDH2 mutations, the overall response rate was 75.4% in venetoclax versus 10.7% in the control group. In the FLT3 mutation group, the incidence was 72.4% and 36.4%, respectively. Among NPM1 patients, 66.7% and 23.5%, respectively; The proportions of TP53 group were 55.3% and 0%, re-

spectively. Combination treatment with azacitidine plus venetoclax was superior to azacitidine alone. This trial provides strong evidence that azacitidine combined with venetoclax can effectively treat AML.

The above trials have proved the safety and efficacy of venetoclax combined therapy for AML patients. High remission rate and low early mortality combined with rapid and long-lasting remission make the combination therapy an attractive and novel treatment for older adults who can't tolerate intensive chemotherapy.

Application of BCL2 inhibitors in elderly patients with non-Hodgkin lymphoma(NHL)

Preclinical trials of BCL2 inhibitors in NHL

(1) Monotherapy

In vitro studies [17], ABT-199 showed single-agent cell-killing activity against some kind of non-Hodgkin's lymphoma (NHL) cells, including DLBCL, FL or MCL. In addition, sensitivity to ABT-199 is highly correlated with BCL2 expression.

(2) Combination therapy

A preclinical trial [18] showed that combination therapy with bevacizumab and venetoclax for 2 weeks can significantly inhibit the growth of non-Hodgkin's lymphoma cells in vitro and in vivo.

Clinical trials of BCL2 inhibitors in NHL

(1) Monotherapy

The first phase I study in NHL patients [19] recruited 106 patients in which 70 patients were treated in dose-escalation cohorts (200 to 1,200 mg). 36 patients (DLBCL, n = 21; FL, n = 15) were treated in the safety expansion cohort (1,200 mg). The median age is 66 years old.

(2) Combination therapy

A phase II study tested Ibrutinib plus Venetoclax in 24 patients with Mantle-Cell Lymphoma [20]. The median age of the patients is 68. Half the patients had a TP53 mutation. The rate of complete response was 71% overall. 42% of patients achieved CR, higher than the historical outcome of ibrutinib monotherapy with 9%. A noteworthy adverse event was tumor lysis syndrome in 2 patients.

A phase Ib dose-escalation study [21] showed promising results in NHL patients treated with venetoclax, bendamustine, and rituximab. Patients in this trial contained 32 with follicular lymphoma, 22 with diffuse large B-cell lymphoma, and 6 with marginal zone lymphoma. The median age is 62. The ORRs for all patients was 65%. Among them, 18 (30%) patients achieved CR, and 21 (35%) achieved PR. Considering the data by histologic subtype, ORRs of 75%, 100%, and 41% were observed in FL, MZL, and DLBCL patients, respectively. Better efficacy was observed for the indolent FL and MZL subtypes of NHL, compared with the aggressive DLBCL form. The

results were better in all subtypes of NHL patients comparing with monotherapy. This study demonstrated the acceptable safety profile in venetoclax plus BR in NHL patients.

A phase I study [22] explored the effect of combined application of ketoconazole (CYP3A inhibitor) on venetoclax by measuring blood drug concentration. 12 NHL patients with a median age of 71.5 participated in the trial. Comparing to venetoclax alone, treatment with oral ketoconazole increased venetoclax mean C_{max} and AUC_∞ by 2.3- and 6.4-fold, respectively. Venetoclax plus ketoconazole resulted in a significant increase of venetoclax exposures, strongly suggesting that CYP3A plays an important role in the elimination of venetoclax. This suggested that attention should be paid to the dosage adjustment of venetoclax when applying two drugs simultaneously.

R-chop regimen is the standard treatment for non-Hodgkin's lymphoma. A phase Ib/II trial [23] explored the effects of venetoclax ranging from 200 to 800 mg once daily orally on 21 days per cycle plus standard cycles of R- or G-CHOP in NHL patients. Fifty-six patients were recruited with the median age of 60.3 and 61.1, respectively. ORR was 87.5% in total. 79.2% and 78.1% patients achieved CR, respectively. Most double-espresso (BCL2+ and MYC+) DLBCL patients (87.5%; n=7/8) achieved CR. Venetoclax addition to R- and G-CHOP was shown to significantly increase direct cell death.

A retrospective, off-label, cohort study evaluated venetoclax in relapsed/refractory NHL patients [24]. The 34 included patients divided by subtype were as follows: 13 high-grade B-cell lymphoma/diffuse large B-cell lymphoma, 10 mantle cell lymphoma, 5 transformed follicular lymphoma, 2 Richter transformation, 2 marginal-zone lymphoma, 1 follicular lymphoma, and 1 post-transplant lymphoproliferative disorder. The median age was 64 years among them. The overall response rate was low in this real-world cohort. Best ORR for this cohort was 26% (n = 9; n =1 CR) and 35% (n=12) had stable disease. While on venetoclax, radiation (n = 18) and other systemic anti-neoplastic therapy (n=26) were also given. In addition to Venetoclax, rituximab was used in 18% (n=6) of patients. A combination of venetoclax and rituximab resulted in CR in a patient with DLBCL. The incidence of adverse events was higher than in clinical trials (76%).

Application of BCL2 inhibitors in elderly patients with MM

Monotherapy

An open-label, dose-escalation, phase I study [25] tested venetoclax in patients with relapsed/refractory t (11;14) multiple myeloma. Sixty-six patients with a median age of 63 years were enrolled, of whom dose-escalation cohorts and 36 in the safety expansion. Thirty (46%) patients were positive for t (11;14). 17 patients [9 with t (11;14)] were given dexamethasone after the disease progression. Among all patients, 14/66 (21%) achieved an overall re-

sponse (PR or better) on venetoclax monotherapy. Among them, 10 (15%) achieved a very good partial response or better (\geq VGPR). Patients with a high BCL2:BCL2L1 gene expression showed better results. This favorable BCL-2 expression was more frequent in the t (11;14) than in the non-t (11; 14) subgroup (38% vs 5%, respectively). Patients in the t (11; 14) subgroup had the same median (9.7 months) as the general population but showed a longer median TTP (6.6 months versus 2.6 months).

Combination therapy

In 2017, an open-label phase Ib study [26] investigated the venetoclax combined with bortezomib and dexamethasone in the treatment of recurrent/refractory multiple myeloma. This combination of drugs showed acceptable safety and tolerability. High response rates (68% ORR and 40% \geq VGPR) were reported and acceptable safety and tolerability were showed. Patients who were nonrefractory to bortezomib and who had received 1-3 prior lines of therapy showed better results (97% ORR and 73% \geq VGPR). In this study, clinical responses were observed to be independent of t (11;14) status.

A randomized, double-blind, multicentre, phase 3 trial [27] in 2020 explored the efficacy of venetoclax combining bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma. 291 patients were randomly assigned to an experimental or control group on a 2:1 ratio. The median age was 66 (IQR: 60-73). Median progression-free survival in the venetoclax group was significantly longer than in the placebo group (22.4 months and 11.5 months, respectively). As with remission rates, the venetoclax effect on progression-free survival appeared to be particularly pronounced in the subgroup of multiple myeloma patients with t (11:14), because these patients have the longest progression-free survival. Although venetoclax prolonged progression-free survival, the trial also showed an increased risk of infection in patients. It is worth noting that the venetoclax group showed a higher mortality rate than the placebo group. This separation appears early in the treatment process. The leading cause of death is infection. The total and serious infection rates were similar in both groups. However, more fatal infections [8 cases (4%)] were reported in the Venetoclax group than in the placebo group (none). Subset analyses showed that the increased mortality occurred mainly in patients without t (11:14) translocation, especially in those with abnormal high-risk cells, and in those with low BCL2 expression. The authors hypothesized that venetoclax's immunosuppressive effects on lymphocytes or other functional effects might exacerbate the immunosuppressive effects of bortezomib and dexamethasone, making patients more susceptible to infection. However, the specific mechanism needs further study. This trial suggests that further screening of patients with this combination of drugs should be performed to avoid risk and ultimately achieve individualized treatment.

Application of BCL2 inhibitors in elderly pa-

patients with MDS

Monotherapy

GX15-070/obatoclax is a nonselective pan BCL-2 inhibitor that can induce apoptosis of AML cell lines and primary samples [28]. A phase II, the multicenter, open-Label study tested obatoclax mesylate in patients with previously untreated myelodysplastic syndromes with anemia or thrombocytopenia [29]. The median age of all 24 patients is 74 years. Patients who received 60 mg obatoclax over 24 hours every 2 weeks showed good tolerance to the drug. Unfortunately, the effectiveness of this single-agent regimen is limited. Although 12 (50%) patients achieved disease stabilization and maintained for 3 months, hematologic responses were achieved in only 2 patients.

Combination therapy

A retrospective study analyzed 20 patients with MDS who received treatment with venetoclax and HMA [30]. The median age is 66 years. For the total cohort, the ORR was 75% (n=15) which was higher than the previously reported response rates in patients treated with HMA alone [31]. 5% (n=1) of patients achieved a CR, 60% (n=12) of patients achieved mCR, and 10% (n=2) of patients achieved a PR. Although the combination therapy showed encouraging results, the cohort also highlighted the myelosuppressive effects of venetoclax, suggesting that the dosage of venetoclax combined with HMA needs further discussion.

Another retrospective study also evaluated the efficacy of venetoclax combined with HMA [32]. 44 patients were recruited in this cohort, 82% of whom were over 60 years old. The overall response was 59% in total, including 14% with a complete response (CR), 27% with a marrow CR with hematologic improvement (HI), and 18% with a marrow CR without HI. The study also highlighted that the combination therapy led to a high rate of alloSCT in 62% of all responders, which is noteworthy because alloSCT was associated with prolonged survival. This retrospective real-world data indicated that adding venetoclax may salvage patients failing to respond to HMA, thus buying patients more time and opportunities to proceed to alloSCT.

Conclusion

As a new type of targeted drug, BCL2 inhibitor has a good inhibitory effect on blood malignant tumor cells. The BCL2 inhibitor is generally well-tolerated in the elderly, with febrile neutropenia being the most common serious adverse event. Tumor lysis syndrome is a serious adverse reaction, but it has rarely been reported in clinical trials. Compared with obatoclax, the new generation of BCL2 inhibitor venetoclax showed better antitumor activity and lower adverse events in patients. Venetoclax exhibits superior efficacy when used in combination with other therapies than when employed as a single agent.

In old patients with relapsed or refractory hematological malignancies, the inclusion of venetoclax in therapy may lead to the possibility of alloSCT. Real-world data showed extensive heterogeneity in the venetoclax dose-escalation, multidrug combination, and time to start treatment, which required further study. BCL2 inhibitors showed better efficacy in patients with certain gene mutations in all hematological malignancies, suggesting that further identification of BCL2 inhibitor sensitive populations and the implementation of individualized treatment may further improve patient survival. In conclusion, Venetoclax showed promising efficacy in elderly hematological malignancies. It is believed that with further research, treatment using Venetoclax will become more accurate.

Declarations

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